Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2019-2020

1. Host team :

Research Unit (e.g. Department or Institute) : Myology Research center
Research Unit Director : Bertrand Fontaine
Research Team Director : Laure Strochlic
Team name : Neuromuscular connectivity in health and diseases (NMCONNECT)

Address : 105 Boulevard de l'hôpital 75013 Paris

Supervisor of the Research Intern for this project : Laure Strochlic
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2. Internship project title:

Molecular determinants of Wnt-induced trans-synaptic function during neuromuscular junction development and maintenance.

3. Internship Description :

The precise control of synaptic connectivity is essential for the development and function of all neuronal circuits. The neuromuscular junction (NMJ) is a tri-partite synapse between motor axons, skeletal muscle fibers and terminal Schwann cells that drives the initiation and control of motion. The accurate alignment of nerve terminals to muscle postsynaptic specializations suggests that an intimate trans-synaptic dialogue occurs between the different cellular compartments. Disruption of this trans-synaptic coordination causes neuromuscular disorders, including congenital myasthenic syndrome (CMS) and auto-immune myasthenia gravis (MG).

In the last decade, several synaptogenic cues have been described to dictate neuromuscular synapse formation. Among these, Wnt morphogens have emerged as critical diffusible signals involved in multiple aspects of the neuromuscular synapse positioning, differentiation and maintenance. At the vertebrate NMJs, our team recently provided evidence that Wnt molecules can interact with the muscle-specific master regulatory kinase MuSK via its Frizzled-Cystein Rich Domain (Fz-CRD) and activate two main pathways: the canonical, ß-catenin-dependent, signalling pathway and the Vangl2-dependent non-canonical Planar Cell Polarity (PCP) pathway (Messéant et al., 2015; Messéant et al., 2017, Boex et al., 2018). But how the Wnt signaling network could regulate neuromuscular connectivity and how it could impact motor function and neuromuscular diseases is unknown.

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This internship project aims to unravel the molecular determinants of Wnt-induced trans-synaptic function during NMJ development and maintenance. Wnt/MuSK interaction stimulates a canonical signaling leading to the transcriptional activation of yet largely unknown synaptic factors, including retrograde signals. Based on a RNA-Sequencing approach performed in synapse-rich muscle regions from mouse with MuSK Fz-CRD deletion, we recently identified several master dysregulated genes coding for regulators of motor axon growth as well as postsynaptic differentiation. The candidate will use cellular and molecular approaches to validate one selected candidate protein and to characterize the signature of this protein *in vivo* during NMJ development and maintenance using a wide range of techniques including molecular and cellular biology (muscle and motoneuronal cell culture/co-culture, lentivirus or adeno-associated virus (AAV) particles delivery of small interference RNAs or cDNA), biochemistry, microscopy (epifluorescent and confocal) and electrophysiology approaches.
Applicants should be enthusiastic with a strong background in cell biology, biochemistry and microscopy. An interest in neurobiology of synapses is highly desirable.